CHEMICAL AND SPECTRAL STUDIES OF MODIFIED STEROIDS

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the Degree of

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IN

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The dissertation entitled 'Chemical and spectral studies of modified steroids [illegible] by Mr. Shahid Akhtar Ansari is suitable for submission for the degree of Master of Philosophy in Chemistry.

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Shahid A. Ansari

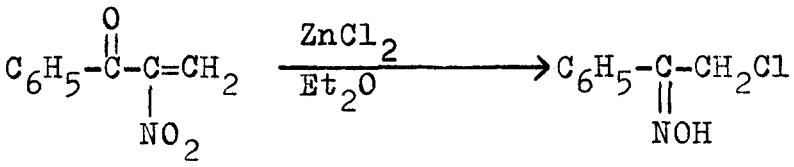
(Shahid A. Ansari).

CONTENTS

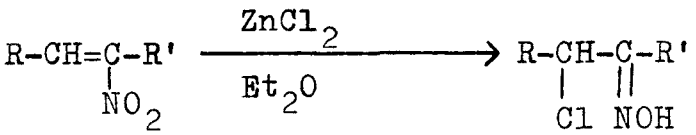
Part-one

THEORETICAL

Attempts have been made to convert nitroolefins directly into oximes. Dornow et al.[1] transformed nitroolefins (I and II a-d) to α-chloro oximes (III and IV a-d) by reduction with Zinc (II) chloride in ether.



(I) (III)

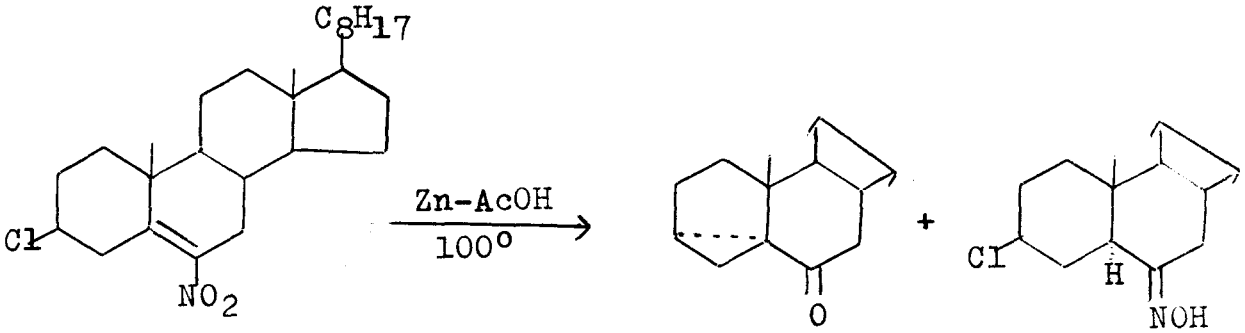


(II) (IV)

	R	R'
a)	CH_3	CH_3
b)	H	C_2H_5
c)	$CH_3(CH_2)_2$	C_2H_5
d)	C_6H_5	CH_3

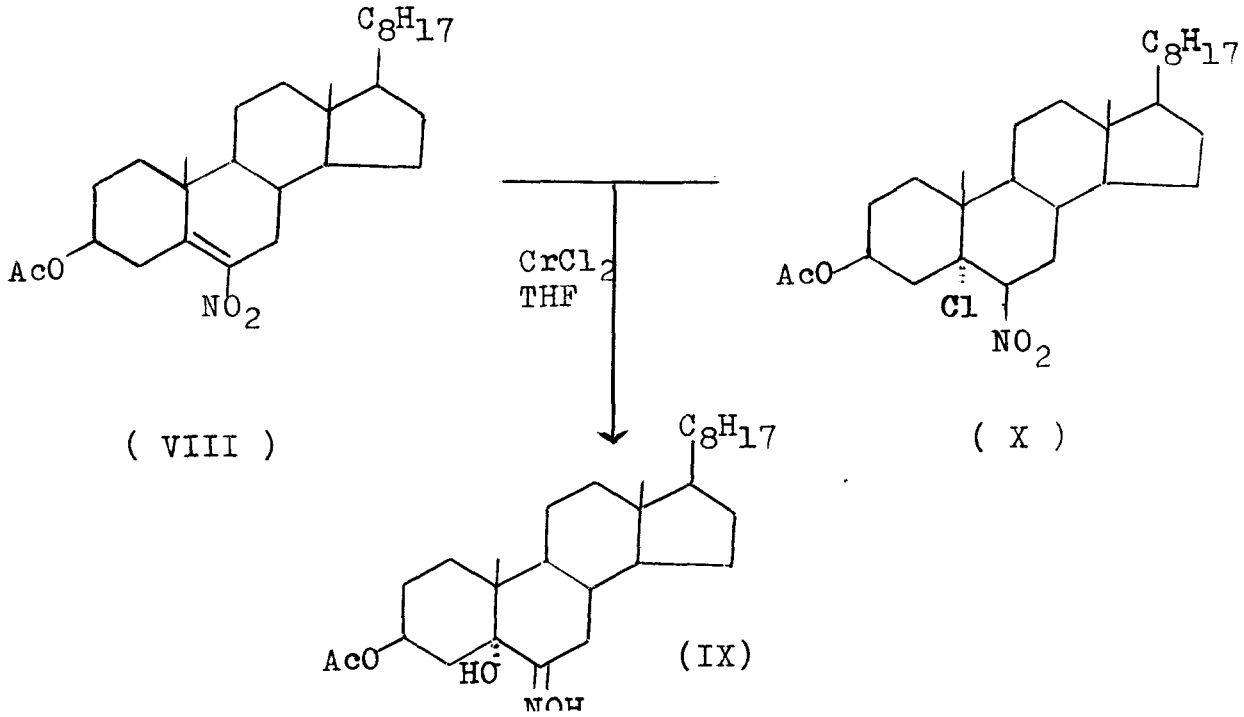
	R	R'
a)	CH_3	CH_3
b)	H	C_2H_5
c)	$CH_3(CH_2)_2$	C_2H_5
d)	C_6H_5	CH_3

Kaye et al.[2] treated 3β-chloro-6-nitrocholest-5-ene (V) with zinc and acetic acid at 100° to obtain 43 % of 3α,5-cyclo-5α-cholestan-6-one (VI) and 20 % 3β-chloro-5α-cholestan-6-one oxime (VII).



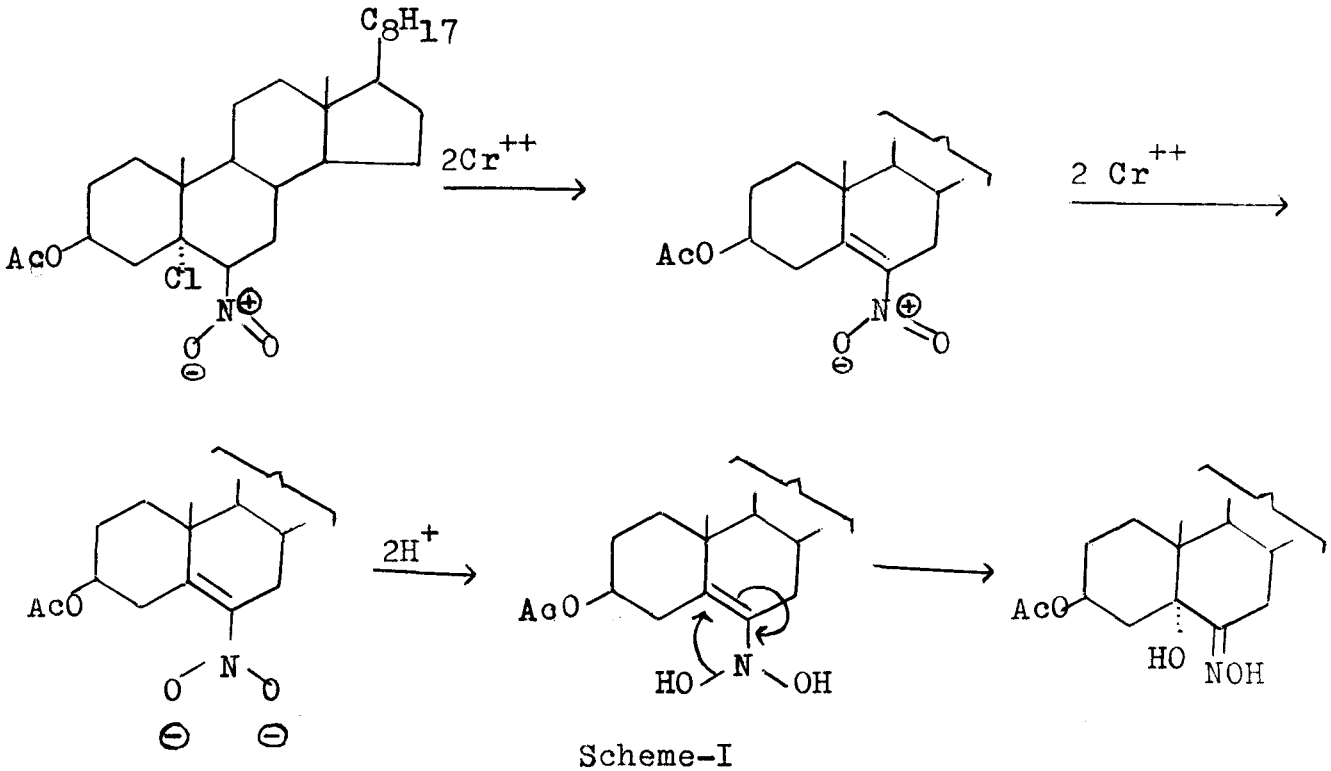
(V) (VI) (VII)

Hanson and Premuzic[3] refluxed a mixture of 6-nitrocholesteryl acetate (VIII) and 0.1 N chromous chloride to get the oxime of 3β-acetoxy-5α-hydrocholestan-6-one (IX) in 80 % yield. 3β-Acetoxy-5-chloro-6β-nitro-5α-cholestane (X) gave the same hydroxyoxime (IX) under an identical reaction conditions.



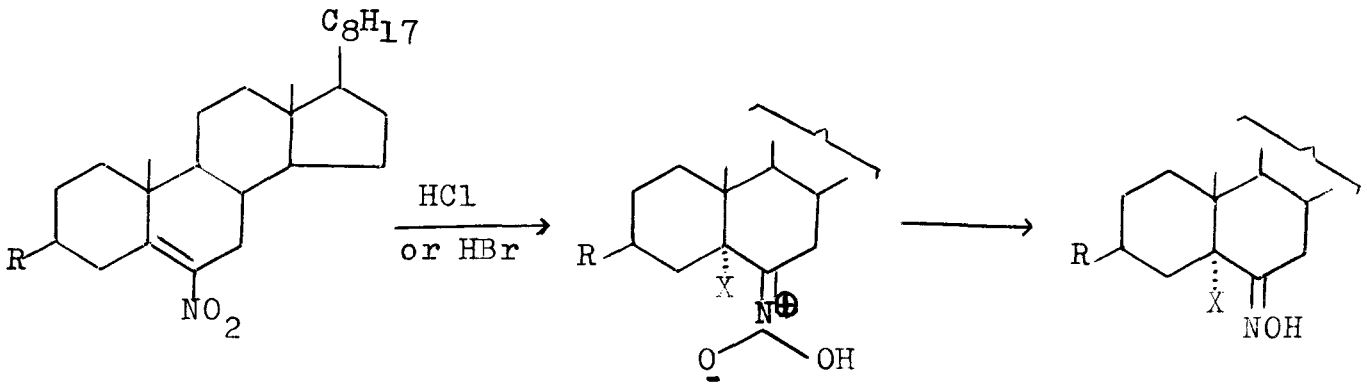
(VIII) (X) (IX)

The mechanism of reduction can be shown as given in scheme[3]-1.



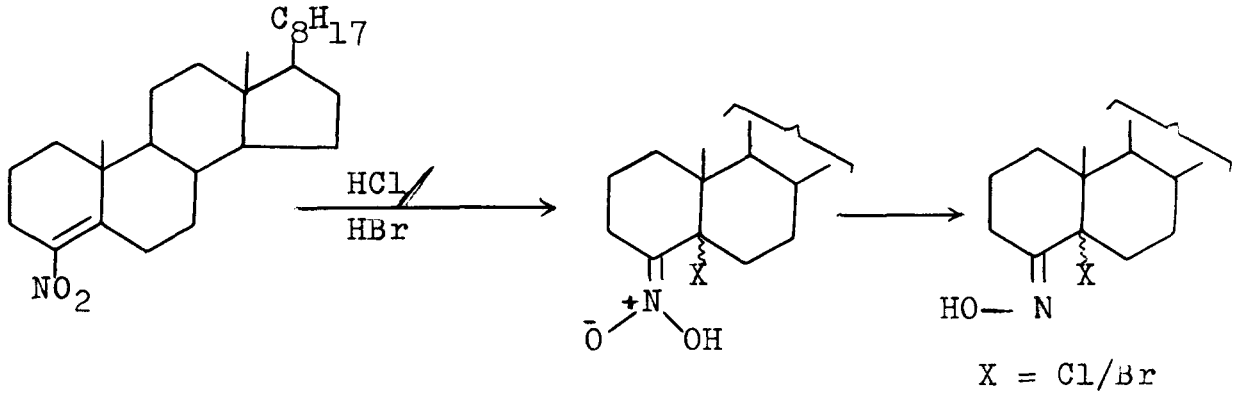
Scheme-I

Reaction of 6-nitrocholest-5-ene (XI a and b) with one mole of hydrogen chloride or bromide afforded 5α-halo-6-oxime (XII a and b) as reported by Komeichi et al[5]. Similarly 4-nitrocholest-4-ene (XIII) gave 5α-halo-4-oxime (XIV).



	R
(XI)	OAc
(XIa)	Cl
(XIb)	H

	R	X
(XII)	OAc	Cl/Br
(XIIa)	Cl	Cl/Br
(XIIb)	H	Cl/Br

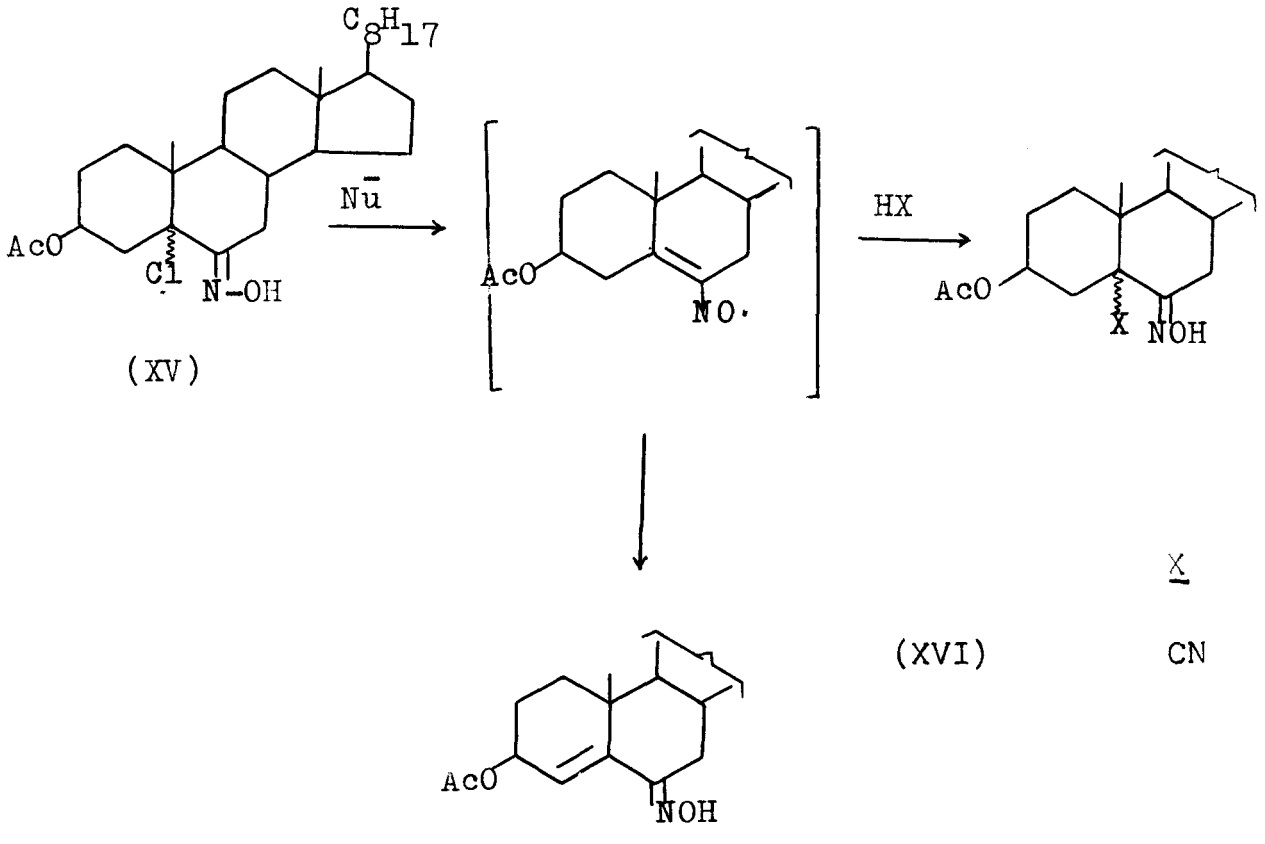


(XIII) (XIV)

The first step of hydrogen chloride or bromide addition to the unsaturated nitrosteroids was considered to give β-halonitronic acid intermediate resulting from 1,4-addition in ordinary way. It was proposed that the initially formed β-halonitronic acid intermediate failed to react with more reagent, and stabilized with loss of oxygen atom to give α-halooxime. To account for this difference, it was postulated that the steric hinderance towards C=N of the intermediate is exerted by the axial halogen, and less effectively, by angular methyl groups, both being two atoms removed from nitrogen and carbon of the C=N grouping respectively[5].

5α-chlorine or bromine can be replaced smoothly with various organic and inorganic nucleophiles to afford high yield of 5α-substituted 6-oxime under mild reaction conditions. Reaction of α-chloro oximes with nucleophiles has received considerable attention.[6-10] Pritzkow et al[6]. have shown that the reaction follows an elimination addition mechanism.

Komeichi et al[11], treated 3β-acetoxy-5α-chloro-6-hydroxyimino-5α-cholestane (XV) with various nucleophiles in dichloromethane to obtain 5α-substituted oximes (XVI).



(XV)

(XVI)

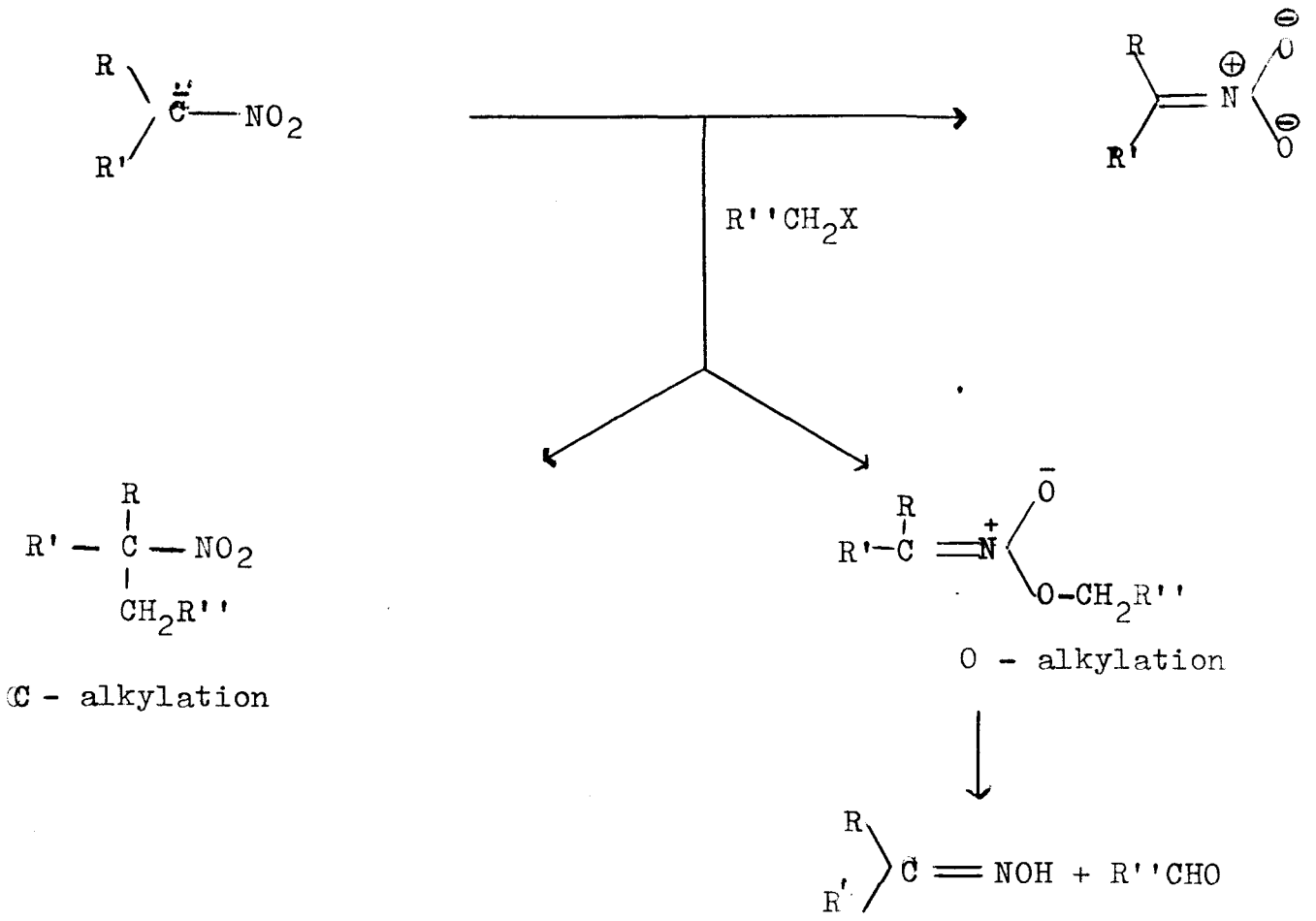
X

CN

(XVII)

The alkylation of nitroalkane anions with alkyl halides may occur on either oxygen or carbon, depending upon the nature of the alkyl halide and reaction conditions[12]. O-alkylation is more usual and gives the carbonyl compound derived from the alkyl halide and the oxime derived from nitroalkane.

In 1966, Kornblum[13] et al. and Russell[14] et al. disclosed that the C-alkylation proceeds by a chain process involving radical anions and free radical[15] as illustrated below for the typical reaction of the sodium salt of 2-nitropropane (XVIII) with p-and O-nitrobenzyl chloride (XIX).



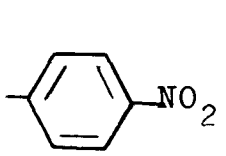
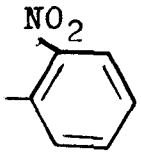
$$ArCH_2Cl \quad + \quad [\,(CH_3)_2\,CNO_2]^- \longrightarrow [ArCH_2Cl]^{\cdot-} + (CH_3)_2\dot{C}\text{-}NO_2$$

(XIX) (XVIII)

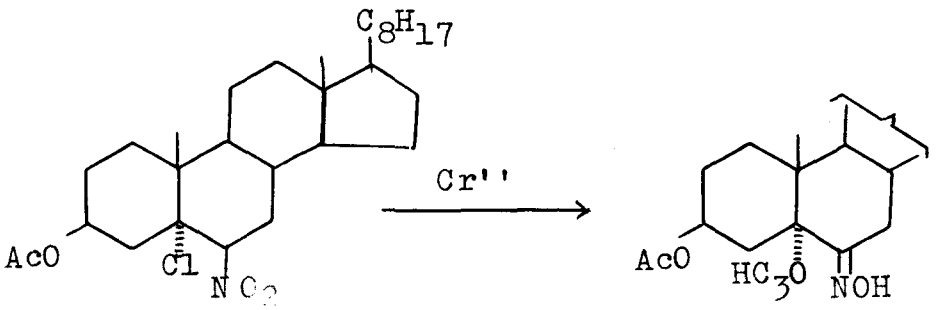
$$[ArCH_2Cl]^{\cdot-} \longrightarrow Ar\dot{C}H_2 + Cl^-$$

$$Ar\dot{C}H_2 + [(CH_3)_2CNO_2]^- \longrightarrow [\,ArCH_2\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}NO_2]^{\cdot-}$$

$$[ArCH_2\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}NO_2]^{\cdot-} + ArCH_2Cl \longrightarrow ArCH_2\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}NO_2 + [ArCH_2Cl]^{\cdot-}$$

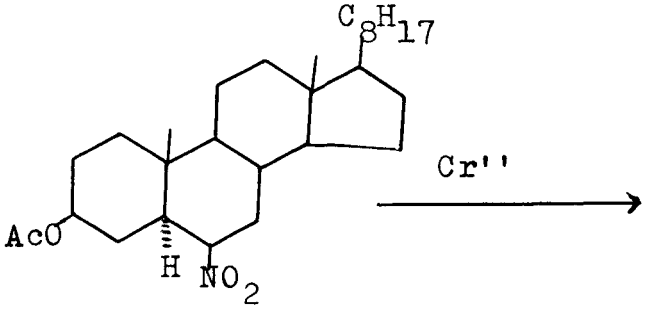
Ar =  , 

Hassner and Heathcock[16] treated 3β-acetoxy-5α-chloro-6-nitrocholestane (XX) with chromous chloride in methanolic hydrochloric acid to obtain 3β-acetoxy-5α-methoxy-6-oximino-cholestane (XXI).

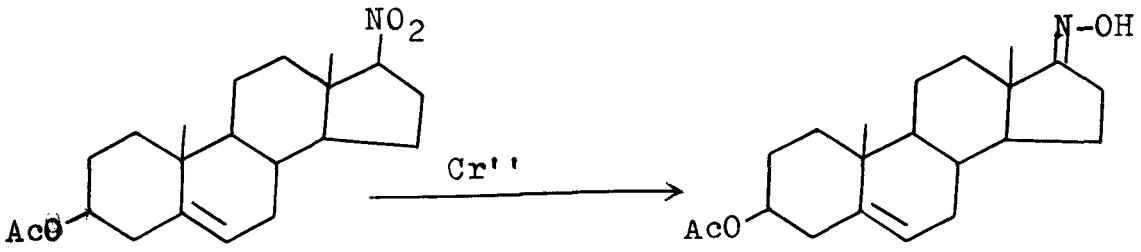


(XX) (XXI)

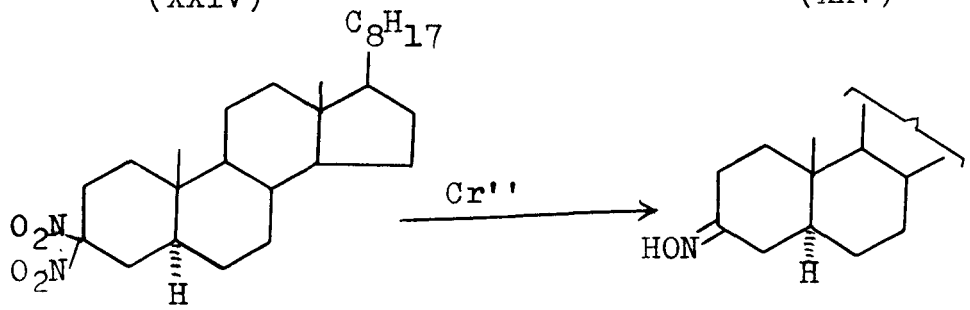
Hanson and Organ[17] carried out the reduction of 3β-acetoxy-6β-nitro-5α-cholestane (XXII) under nitrogen with acedic chromium (II) chloride to give 3β-acetoxy-6-oximino-5α-cholestane (XXIII). 3β-Acetoxy-17β-nitrocholest-5-ene (XXIV) under similar reaction conditions provided oxime (XXV) where as 3,3-dinitro-5α-cholestane (XXVI) afforded oxime (XXVII)[18].



(XXII) (XXIII)

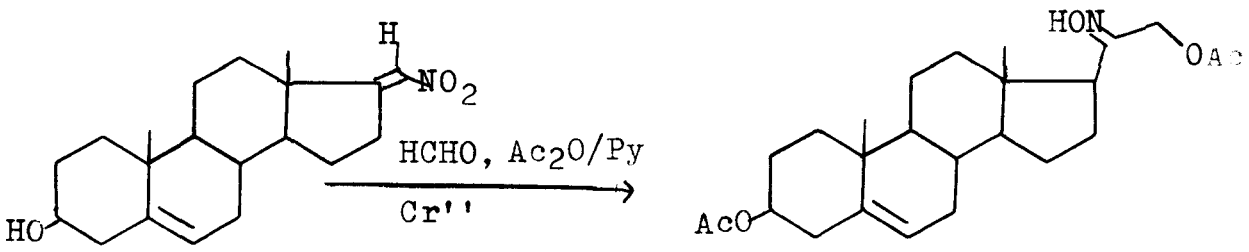


(XXIV) (XXV)



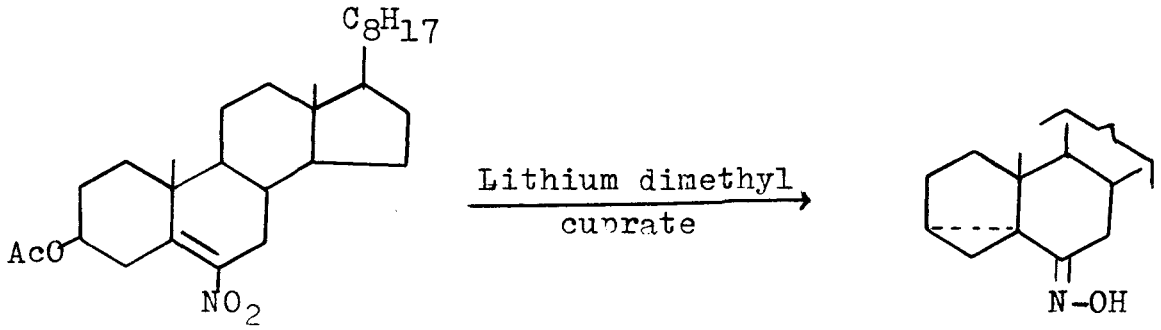
(XXVI) (XXVII)

Barton et al.[19] condensing nitro methylene corticosteroid side chain with HCHO followed by acetylation and chromous chloride reduction obtained corresponding oxime (XXIX).



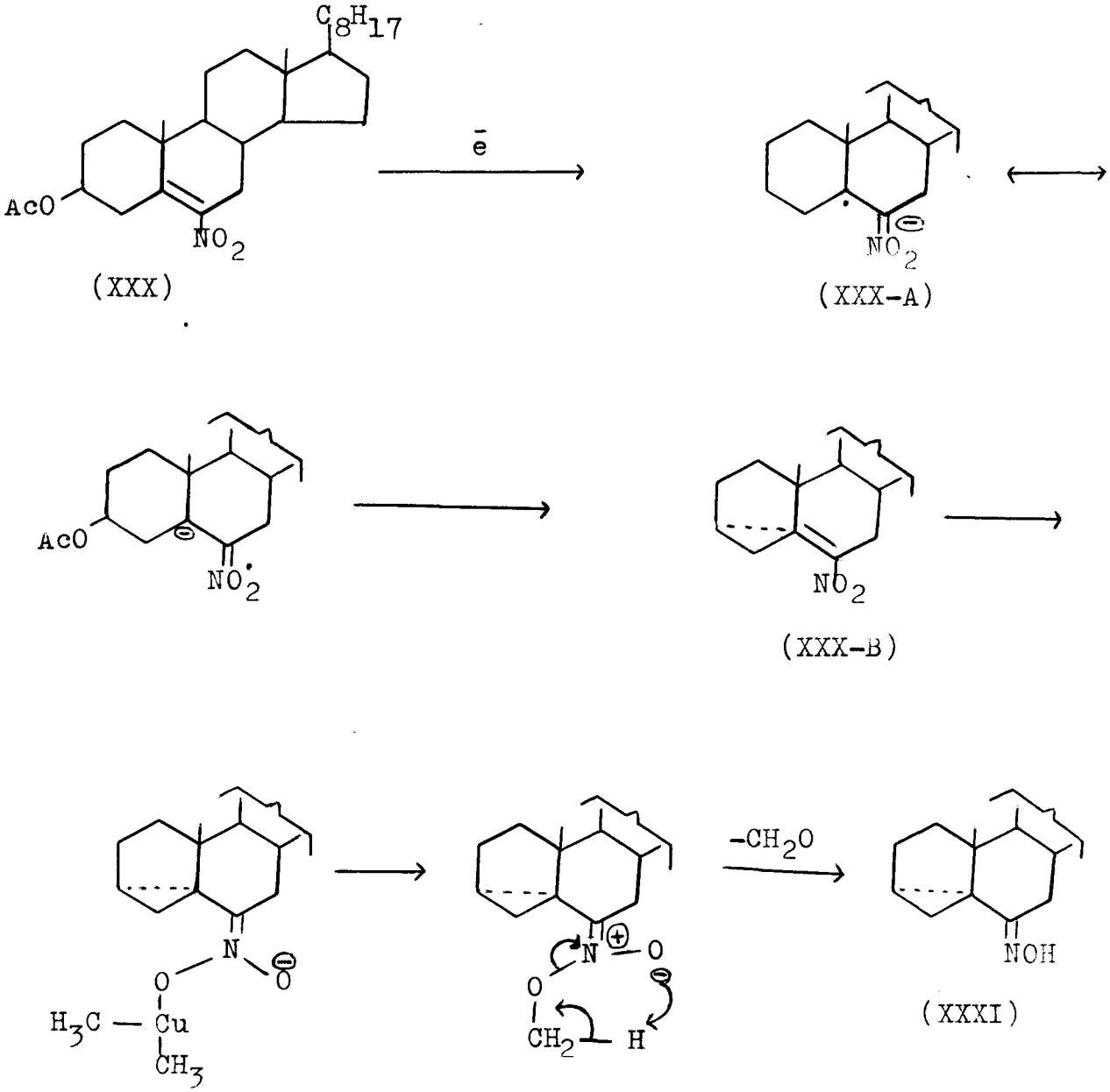
(XXVIII) (XXIX)

Stiver and Yates[20] carried out the reaction of 3β-acetoxy-6-nitrocholest-5-ene (XXX) with an excess of lithium dimethyl cuprate to give 3α,5α-cyclocholestan-6-one oxime (XXXI).

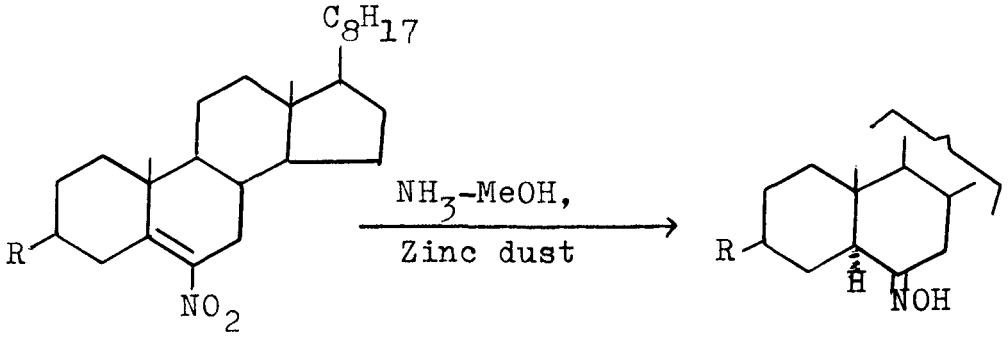


(XXX) (XXXI)

The mechanism for formation of product (XXXI) from (XXX) is proposed as shown in scheme-2. It was suggested that the formation of (XXXI) from (XXX) is initiated by one electron transfer from lithium dimethyl cuprate to give the radical anion (XXX-A). An internal displacement of the acetoxy group in (XXX-A) would be the 3α,5α-cyclo species (XXX-B). The displacement of acetate ion may be faciliated by complexation with lithium or copper species.

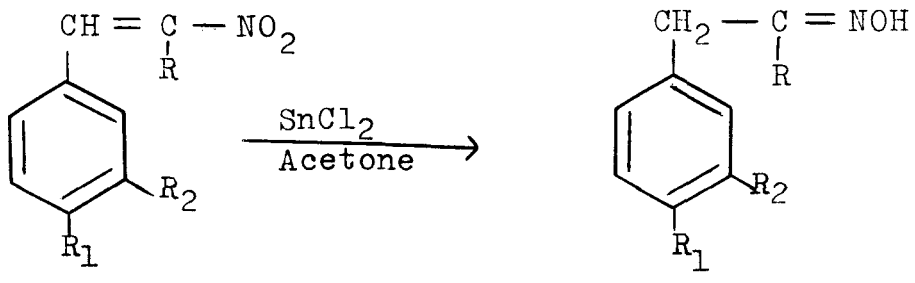


Khan et al.[21] reported the reduction of steroidal 6-nitroolefins (XXXII-XXXV), using ammonia-methanol and zinc dust which afford the corresponding steroidal 6-one oximes (XXXVI - XXXIX) in quantitative yields.



	R		R
(XXXII)	H	(XXXVI)	H
(XXXIII)	Cl	(XXXVII)	Cl
(XXXIV)	OAc	(XXXVIII)	OAc
(XXXV)	OH	(XXXIX)	OH

Verma et al.[22] reported that reduction of nitroalkenes (XL - XLIII) with stanous chloride and obtained corresponding oximes.



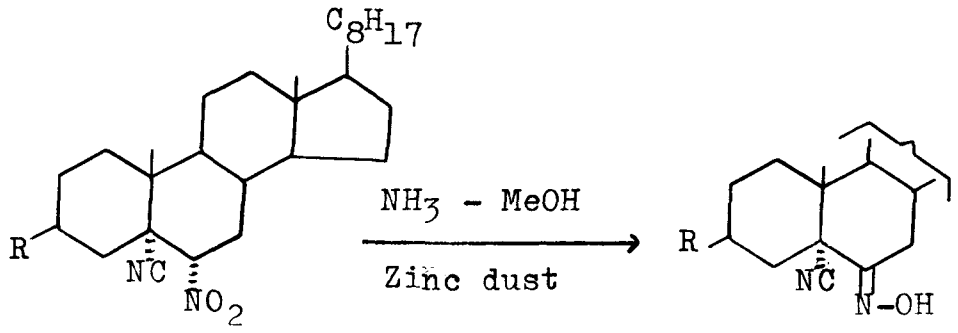
(XL) $R = R_1 = R_2 = H$

(XLI) $R = Me,\ R_1 = R_2 = H$

(XLII) $R = Me,\ R_1 = Br,\ R_2 = H$

(XLIII) $R = Me,\ R_1 = R_2 = OEt.$

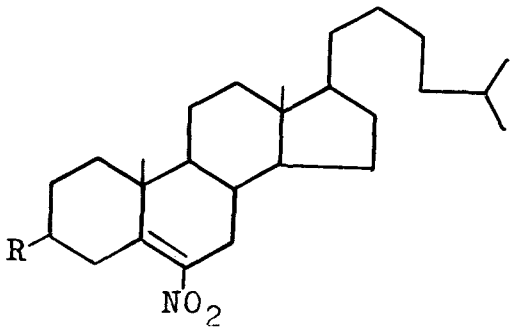
Fazal et al.[23] converted nitrocyanides (XLIV - XLVII) with Ammonia, methanol and zinc dust to the corresponding cyano oximes (XLVIII - LI).



	R = H		R = H
(XLIV)		(XLVIII)	
(XLV)	OH	(XLIX)	OH
(XLVI)	OAc	(L)	OAc
(XLVII)	Cl	(LI)	Cl

DISCUSSION

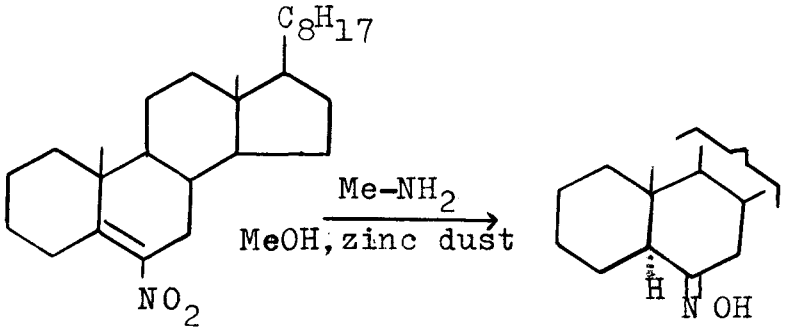
The present work describes the most facile method for the synthesis of steroidal ketoximes from easily accessible steroidal nitroolefins, such as 6-nitrocholest-5-ene (LII), 3β-chloro-6-nitrocholest-5-ene (LIII) and 3β-acetoxy-6-nitrocholest-5-ene (LIV).



	R
(LII)	H
(LIII)	Cl
(LIV)	OAc

Reaction of 6-nitrocholest-5-ene (LII) with methyl amine, methanol and zinc dust :

6-Nitrocholest-5-ene (LII) in ether when treated with methyl amine, methanol and zinc dust provided a compound, m.p. 198°.



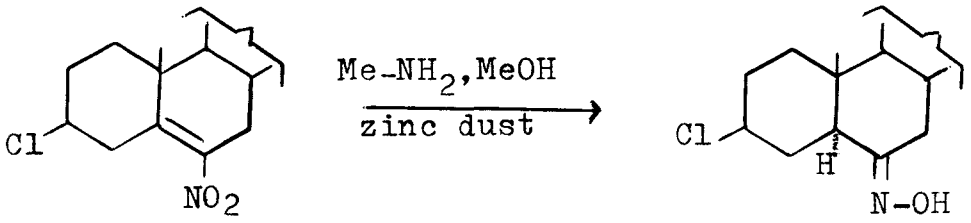
(LII) (LV)

Characterization of the compound (LV), m.p. 198°C as 5α-cholestan-6-one oxime

The compound, m.p. 198° was analysed for $C_{27}H_{47}NO$. Its I.R. spectrum showed bands at 3420-3180 and 1670cm^{-1} which may be assigned to =NOH and C=N stretching frequencies. Its N.M.R. spectrum showed a doublet like signal at δ 3.40 integrating for two protons which may be assigned to C_7-$\underline{H}_2$. A broad singlet at δ 8.3 for one proton which was found exchangeable with D , could be due to the =NO$\underline{H}$ proton. Other signals were observed at δ 1.3 (C10-C$\underline{H}_3$), 0.7(C13-C$\underline{H}_3$), 0.95, 0.9 and 0.7 (other methyl protons). On the basis of above evidences the compound m.p. 198° (reported[24] m.p. 197-98°), was characterized as 5α-cholestan-6-one oxime, which was found identical with the authentic sample of the oxime (mp, mmp, tlc, i.r. and n.m.r.).

Reaction of 3β-chloro-6-nitrocholest-5-ene(LIII) with methyl amine, methanol and zinc dust.

The reaction of 3β-chloro-6-nitrocholest-5-ene (LIII) with methyl amine, methanol and zinc dust under similar reaction conditions afforded a single compound m.p. 174° C.



(LIII) (LVI)

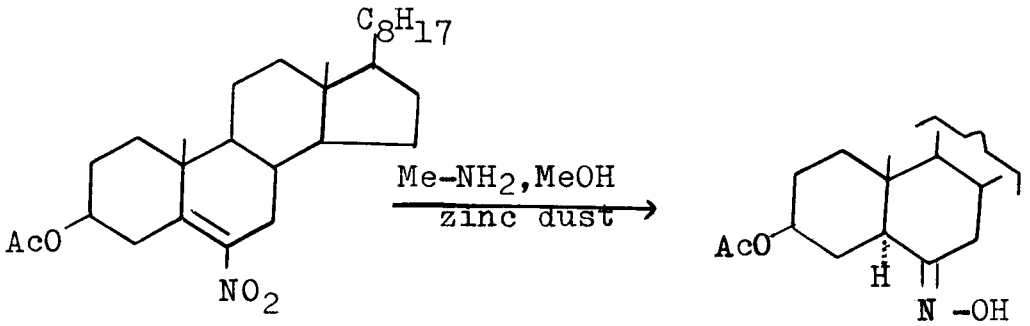
Characterization of compound (LVI), m.p. 174°, as 3β-chloro-5α-cholestan-6-one oxime

The compound m.p. 174° was analyzed for $C_{27}H_{46}NOCl$. It gave positive Beilstein test. Its I.R. spectrum showed bands at 3440-3200, 1680 and 740 cm^{-1} which corresponds to the =N–OH, C=N, and C-Cl stretching frequencies. Its N.M.R. spectrum exhibited a doublet like peak at δ 3.48 for C7-protons and one proton broad singlet at 8.50 (exchangeable with D) for =NOH. A broad singlet at δ 3.6 ($W_{\frac{1}{2}}$=16Hz) integrating for

one proton was assigned to the C3-α$\underline{H}$ (axial). The methyl protons were recorded at δ 1.3(C10-C$\underline{H}_3$), 0.71(C13-C$\underline{H}_3$), 1.15, 0.9 (other methyl protons). On the basis of above spectral data the compound m.p. 174° (reported[25] m.p. 175°C), characterized as 3β-chloro-5α-cholestan-6-one oxime, which was found identical with authentic sample of chlorooxime (mp, mmp, tlc, i.r. and n.m.r.).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene(LIV) with methyl amine, methanol and zinc dust

3β-Acetoxy-6-nitrocholest-5-ene (LIV) on reaction with methyl amine, methanol and zinc dust under similar reaction condition afforded after usual worked up a single compound m.p. 201°.



(LIV) (LVII)

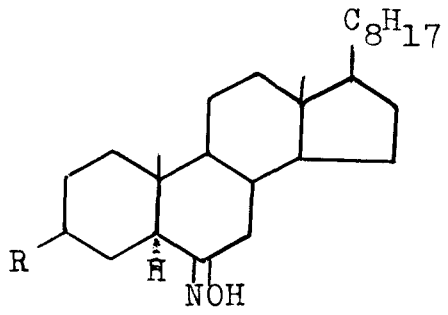
Characterization of the compound (LVII), m.p. 201° as 3β-acetoxy-5α-cholestan-6-one oxime

The compound, m.p. 201° was analyzed for $C_{29}H_{49}NO_3$. Its I.R. spectrum showed bonds at 3450-3140, 1735 and 1680 cm^{-1} assigned to =N-OH, acetate CO and C=N stretching frequencies respectively. The N.M.R. spectrum exhibited a multiplet at δ 5.2 ($W_{\frac{1}{2}}$ = 22 Hz) integrating for one proton which was assigned to C3-proton (axial) and therefore ring junction A and B is trans. A two protons doublet like peak at δ 3.48 (J = 10Hz) for C7-protons and a broad singlet at δ 8.7 for one proton exchangeable with D ascribable to =NO<u>H</u> proton were obtained. Signals for methyl protons were obtained at δ 1.28, 1.2, 0.86, 0.80 and 0.65.

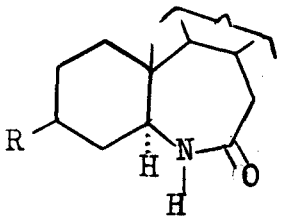
Thus on the basis of spectral values the compound m.p. 201° (reported[26] m.p. 201-202°C) may best be characterized as 3β-acetoxy-5α-cholestan-6-one oxime, which was found identical with authentic sample of 3β-acetoxy-5α-cholestan -6-one oxime (mp, mmp, tlc, i.r. and n.m.r.).

The mechanism of the reaction is under our active consideration.

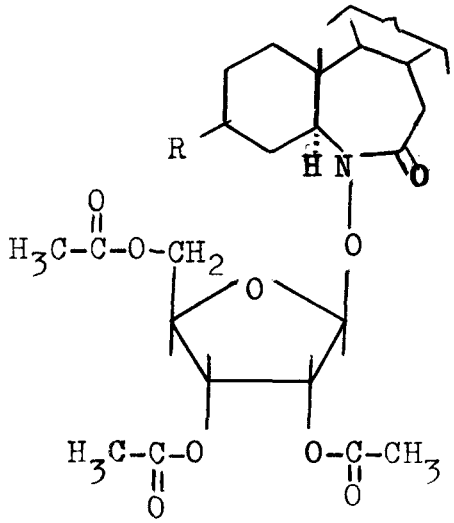
The aim of preparing of the steroidal oximes (LV - LVII) was to convert them into respective lactams (LVIII - LX), for the synthesis of steroidal nucleosides of the type LXI.



	R
(LV)	H
(LVI)	Cl
(LVII)	OAc



	R
(LVIII)	H
(LIX)	Cl
(LX)	OAc



(LXI)

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured with Perkin-Elmer 237 spectrophotometer. N.M.R. spectra were run in CCl_4 on Varian A-60 instrument with T.M.S. as the internal standard. Thin layer chromatographic plate were coated with silica gel G. and sprayed with a 20 % aqueous solution of perchloric acid. N.M.R. values are given in ppm (s, singlet ; d, doublet ; t, triplet ; br, broad ; mc, multiplet centred at) I.R. values are given in cm^{-1}(s, strong; m, medium; w, weak ; br, broad).

3β-chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100 gm) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened the mixture was gently heated at a temperature 50-60° on a water bath for 1 hour and then poured on to crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice-cooled water and air dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (95.5 gm), m.p. 95-96°C (lit.[27] m.p. 96-97°). It gave positive Beilestein test.

Cholest-5-ene

3β-Chlorocholest-5-ene (10 gm) was dissolved in warm amyl alcohol (230 ml) and sodium metal(20gm) was added to the solution with continuous stirring over a period of 8 hrs. The reaction mixture was warmed occasionally. When all the sodium metal was dissolved, the reaction mixture was poured into water, acidified with hydrochloric acid and then allowed to stand over night. A white crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air dried. The crude material was recrystallized from acetone to provide cholest-5-ene as cubes (8.3 gm) m.p. 94° (lit[28] m.p. 95°).

6-Nitrocholest-5-ene (LII)

A suspension of finely powdered cholest-5-ene (6 gm) in glacial acetic acid (50 ml) was vigorously stirred at room temp. and treated with nitric acid (15 ml; d, 1.5) followed by the addition of sodium nitrite (3 gm) over a period of 1 hr. The reaction mixture was poured into cold water and the yellow product thus obtained was extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (10 %) (untill the washing were pink) and again with water and dried over anhydrous sodium sulphate. Removal of the

solvent provided the desired nitro compound as an oil which was recrystallized from ethanol as leaflets (4.5 gm), m.p. 119-120° (lit.[29] m.p. 120-121°).

Reaction of 6-nitrocholest-5-ene (LII) with methyl-amine, methanol and zinc dust : 5α-cholestan-6-one oximes (LV).

To a well stirred solution of 6-nitrocholest-5-ene (1.0 gm) (LII) in ether-methanol (50 ml; 1:1) added methyl amine (15.0 ml, 40 % in H_2O) and zinc dust (3.0 gm) at room temperature. The change of the colour in ~ 1 hr. indicated the completion of the reaction and was monitored by TLC. The reaction mixture was filtered and the filterate was poured in water and extracted with ether. The ethereal solution was dried over sodium sulphate (anhydrous) and evoporated. The residue thus obtained was recrystallized from methanol to give 5α-cholestan-6-one oxime (LV), (780 mg) m.p. 197°C (reported[24] m.p. 197-98°).

$C_{27}H_{47}NO$ requires : C, 80.79; H, 11.72; N, 3.49 .
Analysis found : C, 80.75; H, 11.70; N, 3.50 % ;
I.R. : ν max. 3420-3180 s(=NOH), 1670(C=N) cm^{-1}
N.M.R. : δ 3.4 d(2H, C7-$\underline{H}_2$), 8.3 br(1H, O$\underline{H}$ exchangeable with deuterium), 1.3 s(C10-$C\underline{H}_3$), 0.7(C13-$C\underline{H}_3$), 0.95, 0.8 and 0.7 (other methyl protons).

3β-Chloro-6-nitrocholest-5-ene (LIII).

To a well stirred mixture of 3β-chlorocholest-5-ene (12 gm), glacial acetic acid (80 ml) and nitric acid (25 ml, d, 1.52) at temperature below 20° was added sodium nitrite (6.0 gm) gradually over a period of 2 hours. After the complete addition of sodium nitrite, the mixture was further stirred for about 1 hour. Ice cooled water (200 ml) was added and the yellowish solid thus separated, was filtered and dried. The desired product was recrystallized from methanol as needles (8.3 gm), m.p. 151-152° (lit.[30] m.p. 153°).

Reaction of 3β-chloro-6-nitrocholest-5-ene(LIII) with methyl - amine, methanol and zinc dust : 3β-chloro-5α-cholestan-6-one oxime(LVI).

To a well stirred solution of 3β-chloro-6-nitrocholest-5-ene (1.0 gm) (LIII) in ether-methanol (50 ml; 1:1) added methyl amine (15.0 ml, 40 % in H_2O) and zinc dust at room temperature. The change of colour in ~ 1 hour indicated the completion of the reaction, and was monitored by TLC. The reaction mixture was filtered and the filterate was poured in water and extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate (anhydrous) and evoporated. The semisolid

thus obtained was recrystallized from methanol to give 3β-chloro-5α-cholestan-6-one oxime (LVI),(800 mg), m.p. 173° (reported[25] m.p. 175°C). It gave positive Beilstein test.

$C_{27}H_{46}NOCl$ requires : C, 74.39 ; H, 10.59 ; N, 3.21 .

Analysis found : C, 74.40 ; H, 10.60 ; N, 3.23 % ;

I.R. : ν max. 3440-3200 s(=NOH), 1680 s(C=N) and 740 s(C-Cl)cm^{-1}.

N.M.R. : δ 3.48 d(2H,C7-$\underline{H}_2$), 8.5 br(1H, O$\underline{H}$, exchangeable with deuterium), 3.6 brs(1H, $W_{\frac{1}{2}}$=16Hz, C3-α$\underline{H}$, axial), 1.3 s(C10-C$\underline{H}_3$), 0.71 (C13-C$\underline{H}_3$), 1.15, 0.9 (other methyl protons).

3β-Acetoxy-5-ene

A mixture of cholesterol (100 gm), purified pyridine (150 ml) and freshly distilled acetic anhydride (100 ml) was heated on a steam bath for 2 hours. The reaction was then poured into cold water. The solid thus obtained was filtered and dried. The crude acetate was recrystallized from acetone as find needles (94.0 gm)m.p. 115-116° (lit.[31] m.p. 116°).

3β-Acetoxy-6-nitrocholest-5-ene (LIV)

3β-Acetoxycholest-5-ene (10 gm) was covered with

nitric acid (d, 1.52; 250 ml) and sodium nitrite (10 gm) was gradually added over a period of 1 hour with continuous stirring, slight cooling was also affected during the course of reaction and stirring was continued for additional 2 hours, when a yellow spongy mass separated on the surface of the mixture. The whole mass extracted with ether and washed with water and dried over anhydrous sodium sulphate. The removal of the solvent provided an oil which was crystallized from methanol to provide nitro compound (6.5 gm), m.p. 103° (reported[28] m.p. 102-104°).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (LIV) with methylamine, methanol and zinc dust : 3β-acetoxy-5α-cholestan-6-one oxime (LVII)

To a well stirred solution of 3β-acetoxy-6-nitrocholest-5-ene (1.0 gm) (LIV) in ether-methanol (50 ml; 1:1) added methyl amine (15.0 ml, 40 % in H_2O) and zinc dust (3.0 gm) at room temperature. The change of colour in ~1 hour indicated the completion of the reaction mixture and was also monitored by TLC. The reaction mixture was filtered and the filterate was poured in excess of water and extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate

(anhydrous) and evoporated. The semisolid thus obtained was recrystallized from methanol to give 3β-acetoxy-5α-cholestan-6-one oxime (LVII) (850 mg), m.p. 200°C (reported[26] m.p. 201-2°).

$C_{29}H_{49}NO_3$ requires : C, 75.81 ; H, 10.02 ; N, 3.05 .

Analysis found : C, 75.80; H, 10.0 ; N, 3.04 % ;

I.R. : νmax. 3450-3140 s(=N-OH), 1735 s(CH_3-C(=O)-O), 1680 s(C=N), 1240, 1040 (acetate)cm^{-1}.

N.M.R. : δ 5.2 m(1H, $W_{\frac{1}{2}}$=22Hz, C3-α$\underline{H}$), 3.48 d(1H, J=10 Hz, C7-$\underline{H}_2$), 8.7 brs (1H, -O$\underline{H}$, exchangeable with deuterium), 2.0 s($C\underline{H}_3$-C(=O)-O), 1.28 s(C10-$C\underline{H}_3$), 1.2(C13-$C\underline{H}_3$), 0.86, 0.80 and 0.65 (other methyl protons).

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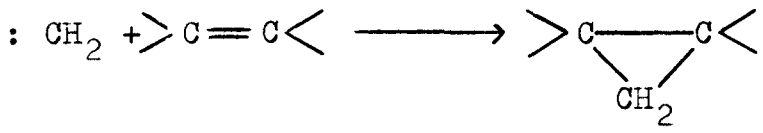
Part-two

THEORETICAL

Reaction of Dihalocarbenes with unsaturated steroids

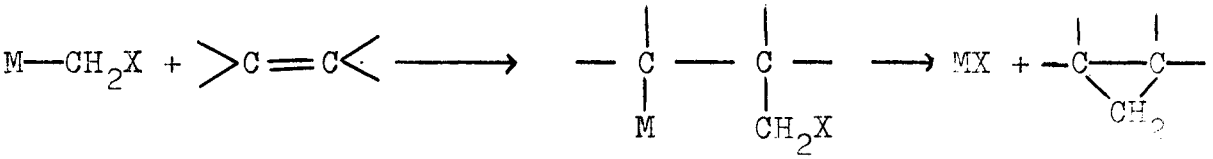
Carbon-carbon single bonds are inert towards methylene even in highly strained small ring compounds such as spiropentane. Carbon-carbon double bonds add methylene easily to form cyclopropanes[1].



Most addition reactions of methylene are stereospecific cis additions, eg; cis-1,2-disubstituted cyclopropanes are obtained from cis-olefins, and trans-1,2-disubstituted cyclopropanes from trans-olefins. The stereospecificity is thought to reflect the singlet state of the reacting methylene (which is not in its ground state). Deviations from stereospecificity, although undesirable for preparative purposes, are of theoretical interest and have received much attention.

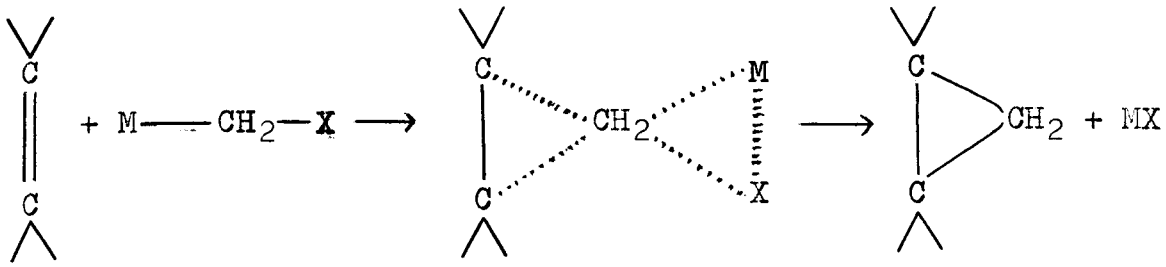
In the synthesis of cyclopropanes, the formation of

complex product mixtures from the competitive addition and insertion of methylene is undesirable. The insertion reaction may be suppressed by 'catalytic' decomposition of diazomethane. Dialkyl aluminium halides, zinc halides, and cuprous halides are suitable catalysts. Cyclopropane formation is thought to proceed via addition of the organometallic compound (I) to the olefin (II) and subsequent elimination of metal halide (III).

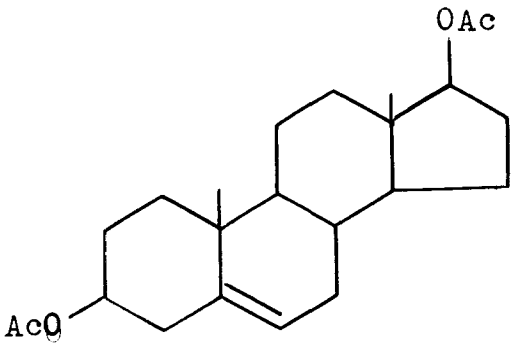


(I) (II) (III)

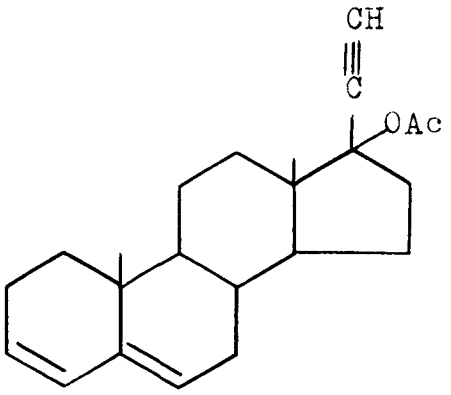
Since the cyclopropane formation is stereospecific, this mechanism implies a well-defined stereochemistry in both the addition and elimination steps, as well as configurational stability of the organometallic intermediate. A three-center reaction involving a one-step displacement of MX from $M-CH_2-X$ by the olefin has been considered.



Dichlorocarbene and diflurocarbene (produced from sodium trichloroacetate and chlorodifluroacetate, respectively) were added to steroids with Δ^2, Δ^3, and Δ^5 unsaturation. Dichlorocarbene failed to add to the Δ^5 double bond of (IV) and similar structures, whereas difluorocarbene was less selective. The discrimination displayed by dichlorocarbene appeares to be due to steric influences. The site of attack by dichlorocarbene changes from the Δ^3 double bond in (V), Both double bonds react with difluorocarbene.



(IV)



(V)

Addition of halogenated methanes to olefins to yield product containing one or more equivalent of halogenated methane was reported by Kharash et al.[2,3] in 1945. In continuation with their interest Kharash et al.[4] again in 1947 reported the addition of carbon tetrachloride, carbon tetrabromide, chloroform and bromoform to a number of olefins containing terminal double bond. These addition readily initiated by small amount of diaceylperoxide or benzoylperoxide or by light of appropriate wave length. The results obtained by Kharash are summarized below in table-1.

In 1950 Oldroyd et al.[5] reported the peroxide catalyzed addition of carbontetrachloride to β-pinene. It was observed that β-pinene readily reacts with CCl_4 in the presence of little as 1 mole percent of catalyst (Bz_2O_2 or Ac_2O_2) to give substantially quantitative yields of a one to one addition product. However, the addition did not take place normally at the two ends of the double bond in β-pinene. Instead, the addition product was still unsaturated possessing one double bond per molecule. Obviously therefore, isomerization must have occurred and the β-pinene must have produced a monocyclic addition product. The chain reaction for production of 7-trichloromethyl-8-chloro-p-menthene is given in scheme-1.

TABLE - I

ADDITION OF CARBON TETRACHLORIDE, CARBON TETRABROMIDE, CHLOROFORM AND BROMOFORM TO OLEFINS

Halide	Olefin	Reaction initiated by (mole % of olefin)	Product	yield(% based on olefin)
Carbon tetrachloride	Octene-I	Ac_2O_2 2	1,1,1,3-Tetrachlorononane	85
	Octene-I	Bz_2O_2 6	1,1,1,3-Tetrachlorononane	75
	Octene-I	Ultraviolet light	1,1,1,3-Tetrachlorononane	..
	Octene-I	Visible light	No reaction	
	Styrene	Ac_2O_2 10	Polymer	
	Ethyl-acrylate	Ac_2O_2 6	Polymer	
	Biallyl	Bz_2O_2 5	Octachlorooctane	
			Tetrachloroheptene	31
	Biallyl	Ac_2O_2 6	Octachlorooctane	31
			Tetrachloroheptene	26
	Propylene	Bz_2O_2	Tetrachlorobutane	a
	Ethylene	Bz_2O_2	Tetrachloropropane	a
Carbon tetrabromide	Octene-1	Ac_2O_2 2	1,1,1,3-Tetrabromononane	b
	Octane-1[c]	Visible light	1,1,1,3-Tetrabromonane	88
	Styrene[c]	Visible light	1,1,1,3-Tetrabromo-3-phenylpropane	96
	Ethylene[c]	Visible light	Tetrabromopropane	a
Chloroform	Octene-1	Bz_2O_2 2	1,1,1-Trichlorononane	22
	Biallyl	Ac_2O_2 8	Trichloroheptene	5

Halide	Olefin	Reaction initiated by (mole / of olefin)	Product	yield(/ based on olefin)
Bromoform	Octene-I	Ac_2O_2 5	1,1,3-Tribromononane	31
	Octene-I	Visible light	No reaction	
	Styrene	Bz_2O_2 5	Phenyl tribromopropane	10
			Low mol.wt. polymers	10

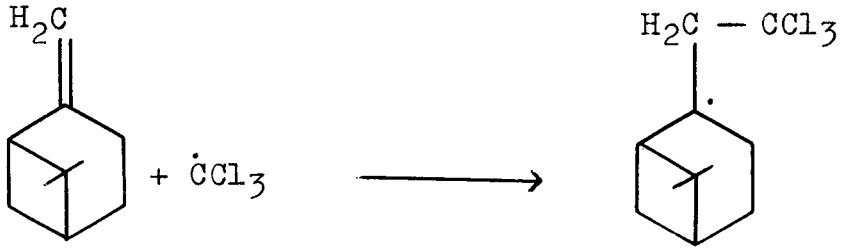
a=The olefin vapour was bubbled into the reaction mixture at atmospheric pressure; under those conditions, most of the olefin escaped from the mixture. Presumably, all of the olefin which was absorbed did react in the expected manner. Better yields have been obtained by carrying out the reactions under pressure and in the absence of oxygen.

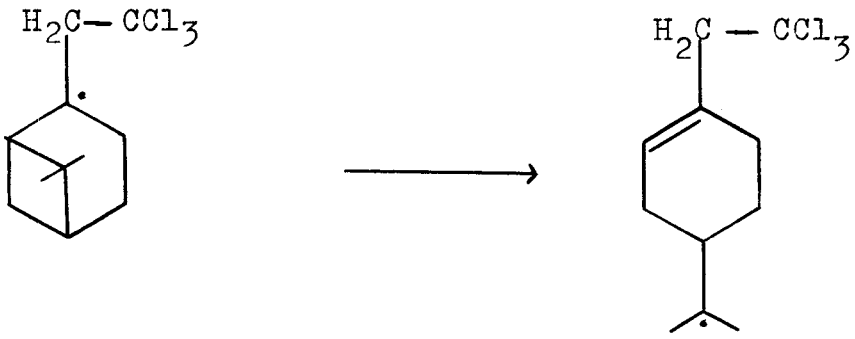
b=The yield was good, but the reaction was so vigorous that some of the product was lost through the condenser.

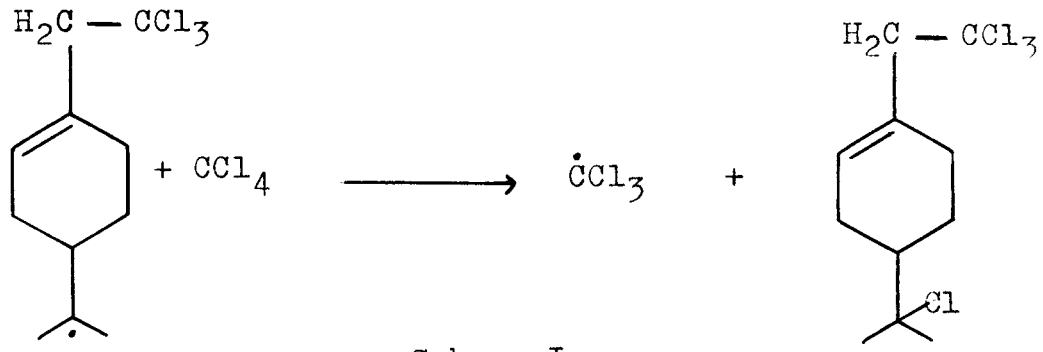
c=Reaction was carried out in carbon tetrachloride as a solvent.

1. Peroxide $\longrightarrow$ $R^{\cdot}$

2. $R^{\cdot} + CCl_4 \longrightarrow RCl + \dot{C}Cl_3$

3. 

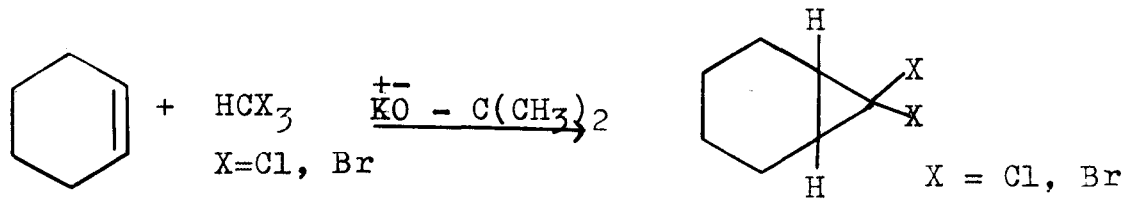
4. 

5. 

Scheme-I

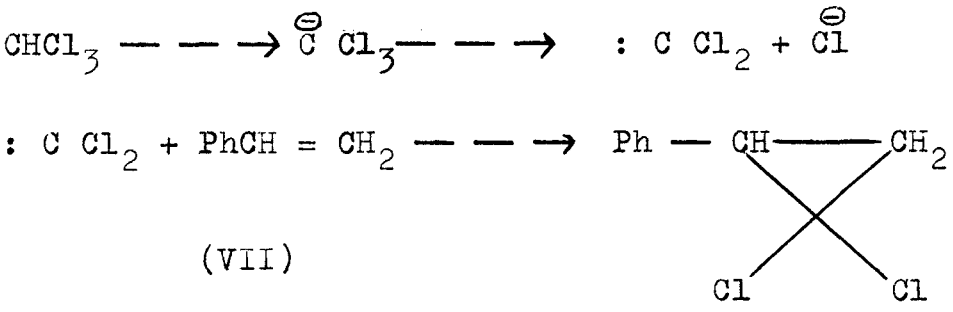
(Proposed chain reaction for production of 7-trichloromethyl-8-chloro-p-menthene).

Doering and Hoffmann[6] demonstrated in 1954 that dichlorocarbene generated from haloforms in the presence of base could be trapped by olefins affording dihalocyclopropane derivatives (VI) in an excellent yields. This reaction represents the first structural evidence for the formation of dichlorocarbene ($:CCl_2$) from chloroform.(scheme-II).



Scheme-II (VI)

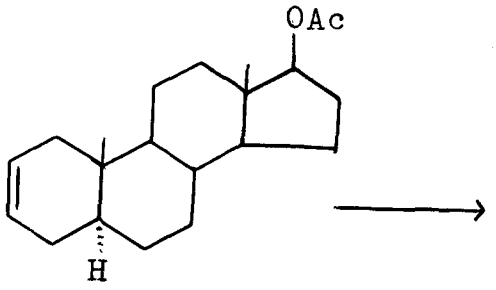
Makosza et al[7]. reported the preparation of dichlorocyclopropane derivatives in an aqueous medium. He carried out the reaction of styrene (VII) with chloroform , aqueous NaOH and TEBA chloride as catalyst gave 1-phenyl-2,2-dichlorocyclopropane (VIII) in an excellent yield. The mode of reaction is proceed via following manner as shown in shceme-III.



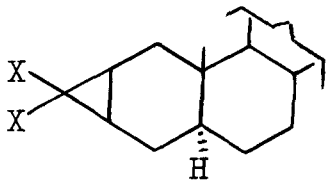
(VII) (VIII)

Scheme-III

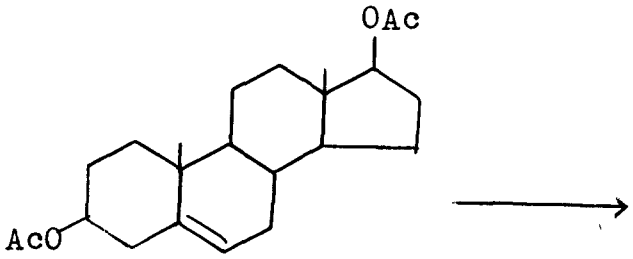
Knox et al.[8] in 1962 described the addition of dichloro and difluorocarbenes to a variety of unsaturated steroids with formation of a heretofore unavailabe class of steroidal cyclopropanes. The result obtained are summarized below.

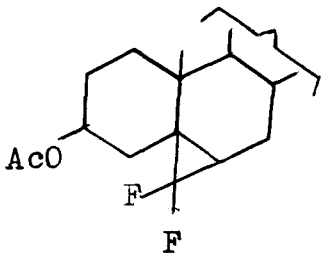


(IX)



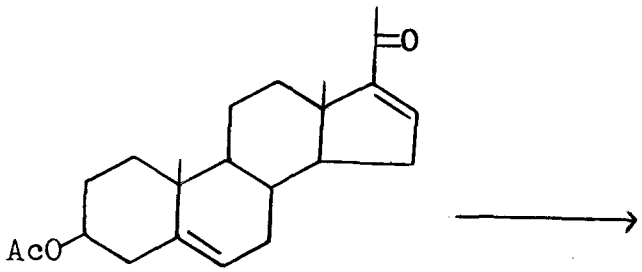
	X
(X)	Cl
(XI)	F

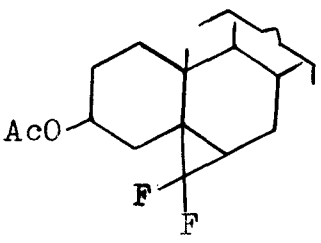




(XII)

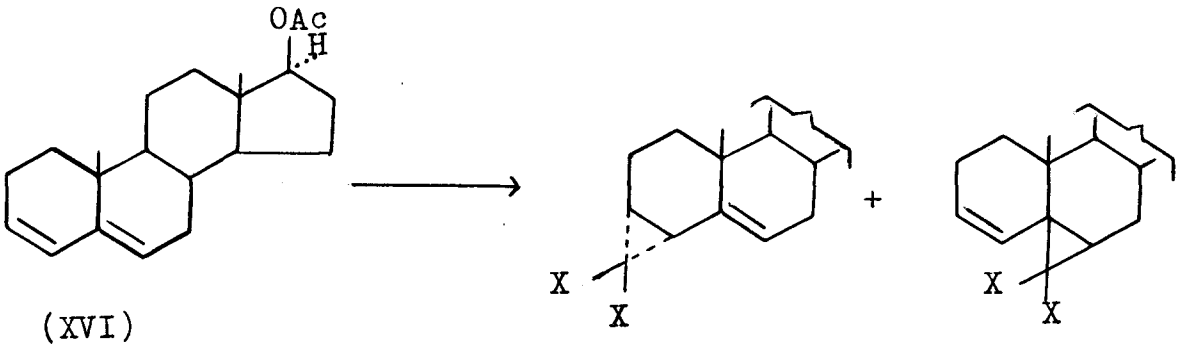
(XIII)





(XIV)

(XV)

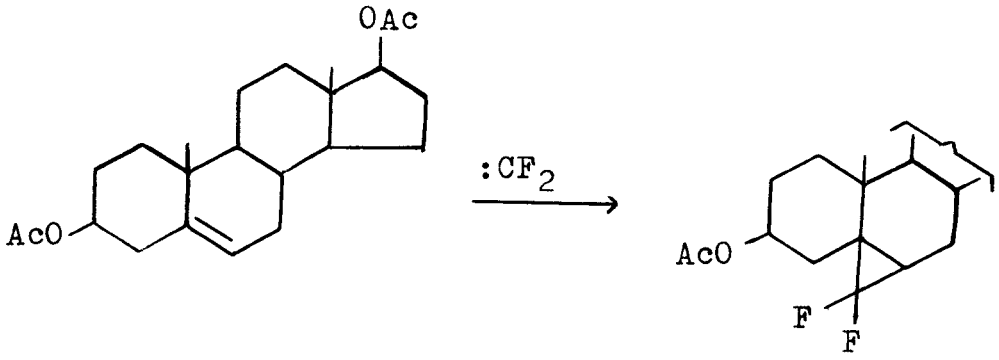


(XVI)

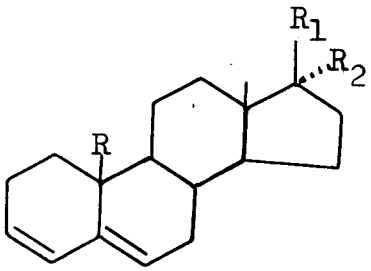
	X		X
(XVII)	Cl	(XIX)	Cl
(XVIII)	F	(XX)	F

In another communication[9] they described the addition of dichloro and difluorocarbene to unsaturated steroids. They also discuss the differences in the relative reactivites of dichlorocarbene towards monoolefinic steroids, conjugated and unconjugated steroidal dienes and the geometry of adducts.

The failure of dichlorocarbene to add to Δ^5 (XXI) or $\Delta^{3,5}$ steroids bearing a 10β-methyl group (XXIII-a,d,g,h) but successful addition to Δ^5 of $\Delta^{3,5}$ nor steroid (XXIII-b,c,e,f) suggested very strongly that the steric requirements of the large dichloromethylene carbene preclude approach to, and electrophilic attack upon the Δ^5 from the β-face of the olefins (XXII).



(XXI) (XXII)



(XXIII)

(a) R = Me, R_1 = OH, R_2 = H

(b) R = R_2 = H, R_1 = OH.

(c) R = H, R_1 = OH, R_2 = C ≡ CH

(d) **R** = Me, R_1 = OAc, R_2 = H

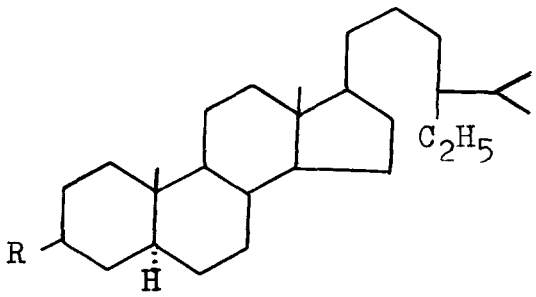
(e) R = R_2 = H, R_1 = OAc

(f) R = H, R_1 = OAc, R_2 = C ≡ CH

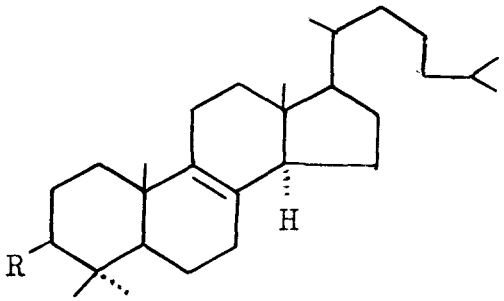
(g) R = Me, R_1 = Ac, R_2 = OH.

(h) R = Me, R_1 = Ac, R_2 = OAc

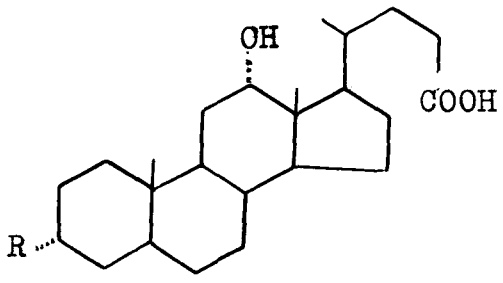
Ikan et al[10], in 1973, reported that dichlorocarbene generated from chloroform, aqueous NaOH and catalytic amount of triethyl benzyl ammonium chloride (TEBA) reacts readily with steroids (XXIV - XXIX) leading to the corresponding chlorides (XXX - XXXV) respectively.



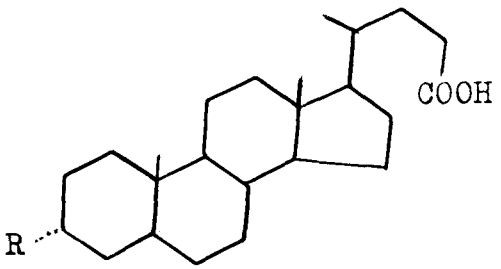
	R
(XXIV)	OH
(XXX)	Cl



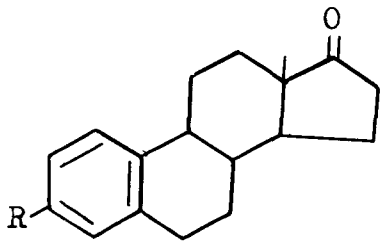
	R
(XXV)	OH
(XXXI)	Cl



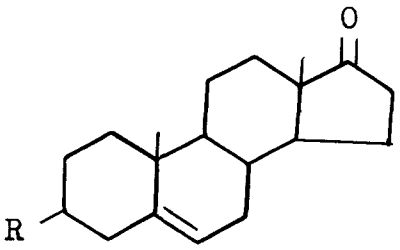
	R
(XXVI)	OH
(XXXII)	Cl



	R
(XXVII)	OH
(XXXIII)	Cl

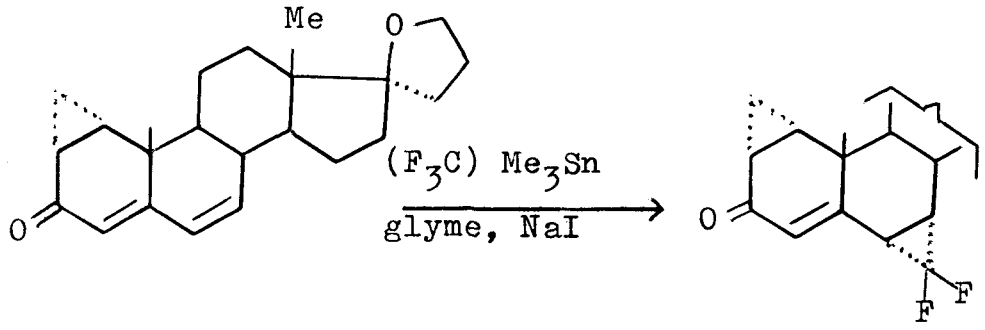


	R
(XXVIII)	OH
(XXXIV)	Cl



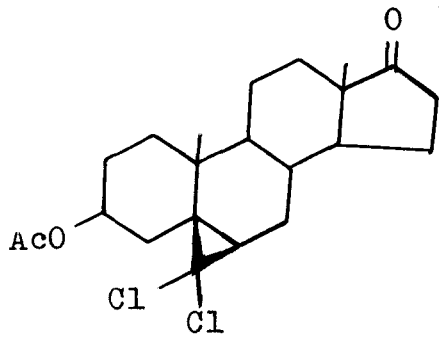
	R
(XXIX)	OH
(XXXV)	Cl

Hinkley et al.[11] reported the formation of spiroxenone (XXXVII) by the reaction of spiroxadienone (XXXVI) with $(F_3C)Me_3Sn$, glyme and NaI.



(XXXVI) (XXXVII)

Bourdream et al.[14] confirmed the structure of (XLIV) by X-ray crystallographic method.

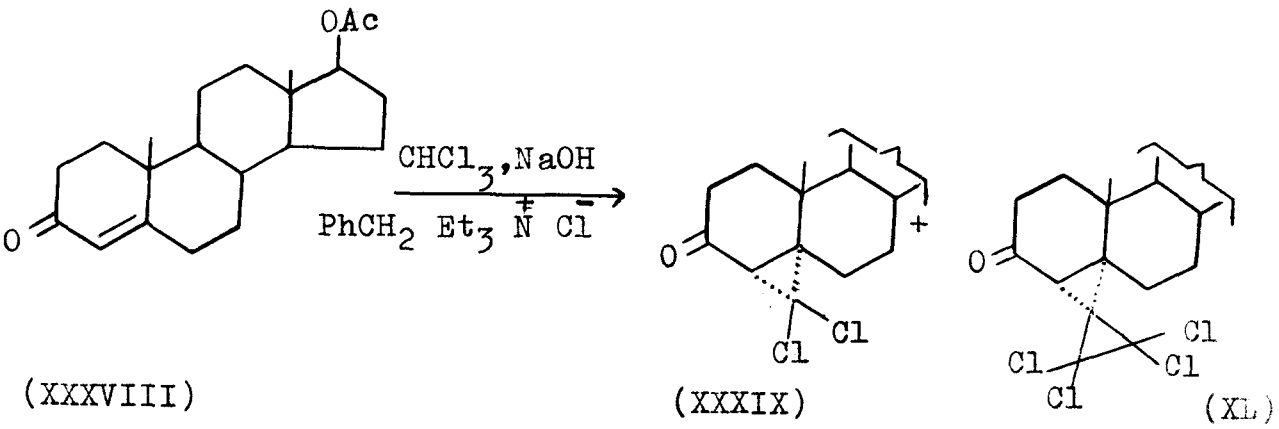


(XLIV)

Prompted with the novel reactions of dihalocarbenes we have started a research project[φ] on the reaction of dichloro and dibromocarbenes with steroidal olefins such as cholest-5-ene (XLV - a) and its 3β-chloro (LXV - b) and 3β-acetoxy (XLV - c) analogues.

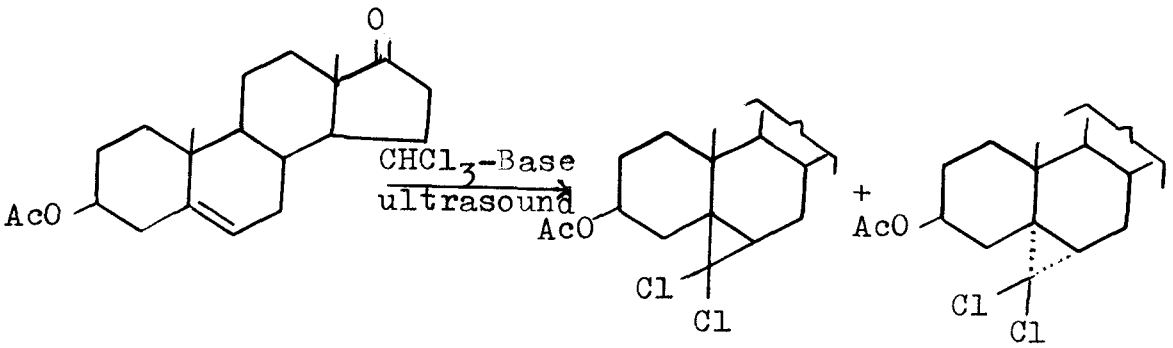
φ This work is started with the collaboration of Dr.G.A.S. Ansari, The University of Texas, Medical Branch, Division of Biochemistry, GALVESTON, TEXAS, 77550 U.S.A.

Dehmlow et al.[12] treated testosterone acetate (XXXVIII) with $CHCl_3$, 50 % NaOH and $PhCH_2Et_3\overset{+}{N}\overset{-}{Cl}$ as catalyst and obtained a mixture of α and β-stereoisomers of dichlorocyclopropyl derivatives (XXXIX) and (XL) .

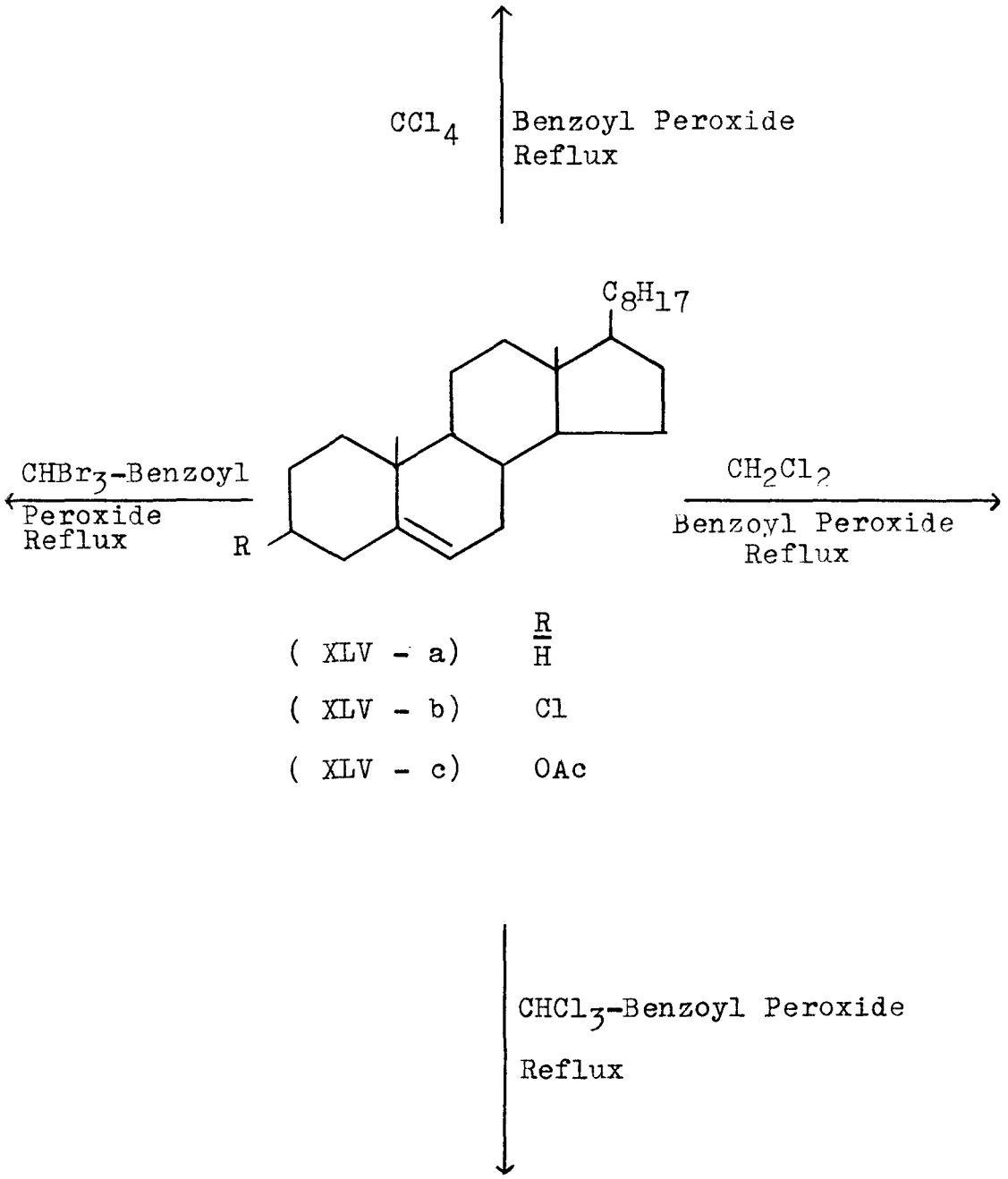


(XXXVIII) (XXXIX) (XL)

Jennings et al.[13] prepared 5α,6α (XLIII) and 5β,6β-dichloromethylene (XLII) adducts of 3β-acetoxy-5-androsten-17-one (XLI) by action of $CHCl_3$ and base under phase transfer conditions using ultrasound agitation.



(XLI) (XLII) (XLIII)



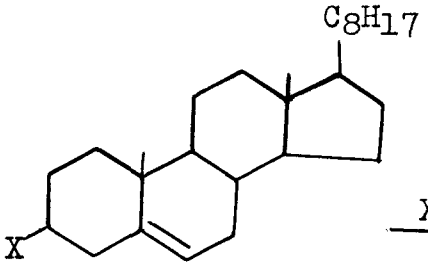
	R
(XLV - a)	H
(XLV - b)	Cl
(XLV - c)	OAc

General Procedure of the Reaction

The steroidal olefins (5.37 gm; 0.25 mole) was dissolved in chlorofom (11.9 ml., 1 mole) and benzoyl peroxide (6.05 gm; 0.5 mole) was mixed together and refluxed on water bath for 10 hours. After the completion of the reaction it was cooled and the chloroform layer was separated, washed with solution of sodium bicarbonate (10 %), sodium thiosulphate solution (5 %) and finally with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oily residue which was chromatographed over silica gel column ($\sim$ 100 gm). The compounds isolated gave positive Beilstein test. The chemical, spectral and biochemical studies of these compounds are under progress.

The similar experimental method is used for the reactions of steroidal olefins (LXV a-c). The results obtained so far are tabulated as below:

Reagents : CCl_4 - Benzoyl peroxide



Solvents of elution			Product
Pet. ether	:	Ether	
18	:	1	X (oil)
8	:	1	Y (oil)

X=OAc

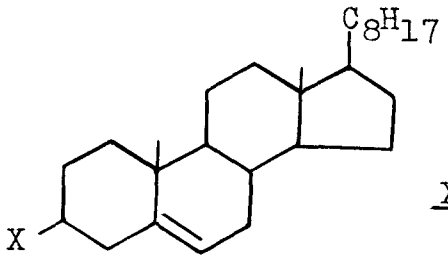
X=H

Solvent of elution	Product
Pet.ether	X (oil)
Pet.ether:Ether	Y (oil)
20 : 1	

X=Cl

Solvents of elution			Product
Pet.ether	:	Ether	X (oil)
18	:	1	
15	:	1	Y (oil)
10	:	1	Z (oil)

Reagents : $CHCl_3$ - Benzoyl peroxide



Product X
m.p. 215°C ← X=OAc

X=H →

Solvents of elution			Product
Pet.ether	:	Ether	
20	:	1	X(oil)
18	:	1	Y(oil)

X=Cl ↓

Solvents of elution			Product
Pet.ether	:	Ether	X (oil)
Pet.ether	:	Ether	
20	:	1	Y (oil)
15	:	1	Z (oil)

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